Remarks

A. Pending Claims

Claims 1 – 16, 21, 31 – 38 and 40 have been cancelled without prejudice. Claims 17 – 30 and 40 stand rejected. Claims 17, 22, 28 and 39 are presently amended. Claims 41 – 80 are new. Claims 17 – 20, 22 – 30, 39 and 41 – 80 are pending in the case.

B. Claim Objections

Claims 22-30 and 39 are objected to for the reasons set forth on page two of the Office action. Applicant has amended claims 22, 25, 28 and 29 for clarification. Withdrawal of the objections is respectfully requested.

B. Rejections Under 35 U.S.C.§102

Claims 17 – 22, 28 and 39 stand rejected pursuant to 35 U.S.C. §102(b), as allegedly being anticipated by U.S. Patent No. 5,854,216 to Gaudreau ("the '216 patent").

Applicant has amended claim 17 to recite, in part "[a] GHRH analogue … having the formula Tyr- D-Ala^{2}-Asp-Ala-Ile-Phe-Thr-Asn- Ser-D-Tyr^{10}-Arg-Lys-Val-Leu- D-Ala^{15}-Gln-Leu-Ser-Ala-Arg-Lys-Lys^{22}-Leu-Gln-Asp-Ile-Met-Ser-Arg-A30-NH_2, wherein A30 is any amino acid sequence of 1 up to 15 residues." Claim 21 has been cancelled without prejudice.

Claims 22, 28 and 39 have each been amended to include the feature "said GHRH analogue or salt consisting essentially of the formula: Tyr-…-A30-NH_2" in addition to the remaining features set forth therein.

Applicant respectfully submits that the '216 patent is silent with regard to a GHRH analogues and formulations having the combination of features set forth in amended claims 17, 22, 28 and 29 and respectfully requests that the 35 USC §102 rejections against the claims be withdrawn.

C. Rejections Under 35 U.S.C.§103

Claims 17 – 30 and 39 stand rejected pursuant to 35 U.S.C. §103(a) as obvious over the teachings of the '216 patent. Applicant respectfully disagrees.

Claims 22, 25, 28 and 39 have been amended to include the feature "a GHRH analogue or a pharmaceutical acceptable salt thereof in an amount effective to stimulate secretion or synthesis of growth hormone in a mammal in need thereof." Support for this amendment may be found in the specification as filed, at least, for example, in paragraphs [0092], [0058] and in FIG. 2 and 3. The '216 patent appears to be silent on at least this feature.

The obviousness rejections appear to rely, at least in part, on the assertion that the '216 patent teaches that some GHRH analogue peptides of formula Ra-X-Rb may be used to treat certain conditions. The passage in questions recites, "[o]ther applications of some of the peptides of the present invention in mammals, especially humans, may be for the treatment of..." (the '216 patent Col. 5, lines 12-37). The '216 patent defines "peptides of the present invention" as Ra-X-Rb, where Ra is a fluorophore, Rb is a peptide moiety having a sequence derived from hGRF(1-29), and where X is a linker covalently coupling the fluorophore to the N-terminal end of the peptide moiety (the '216 patent, Cols. 3-4). The '216 patent appears to be silent however on the use of GRF analogues lacking the Ra-X- portion of the subject peptides. In other words, contrary to the argument set forth in the Office action, the '216 patent does not appear to assert a therapeutic utility for the peptidic moiety alone (i.e., the portion of the analogue corresponding to Rb). Moreover, the mere statement that "some peptides may be used," fails to provide any guidance or suggestion to the skilled practitioner as to which peptides should be developed for therapeutic modality.

The Office action includes the assertion that certain of the claims are obvious in view of the '216 patent's teaching that compound 8 (i.e., [D-Ala^2, D Tyr^{10}, D-Ala^{15}, Lys^{22}]hGRF(1-29)NH_2) "possesses biological activity: the analogue has a binding affinity to the receptor in rat adenopituitary cells equivalent to that of wild type hGRF(1-29)NH2 (Table 11). In addition, Gaudreau teaches that substitutions by D-amino acids increase the *in vitro* and in *vivo* metabolic stability of the peptide (column 24, lines 23-26)." (See Office action, page 6). Applicant respectfully disagrees with this assertion for at least the following reasons.

The presently claimed species to which the Office action refers (namely, "compound 8" in the '216 patent) is referred to in the present application as "compound 5," (see, e.g., Table 1, # 5 of the present application). Table 11 of the '216 patent discloses various *in vitro* properties of GHRH analogues 1-14. Specifically, Table 11 discloses the IC_{50} values and the relative affinities of each of the GHRH analogues for binding sites present on rat anterior pituitary cells (i.e., the relative affinity a human GHRH analogue for the corresponding rat GHRH cell surface receptor). These are the only "biological" data that describe any properties of the specific GHRH species at issue. In fact, compound 8 is not even among those peptides that are further tested for their ability to activate adenylate cyclase activity in cultured cells (see the '216 patent, Table 12, Col. 27, and text corresponding thereto). Therefore, contrary to the assertion set forth in the Office action, there are no "biological data" present in the '216 patent that would indicate to the skilled practitioner that compound 8 displayed any biological activity beyond binding to the rat GHRH receptor. Compound 8 does not appear to have been considered for therapeutic purposes. The '216 patent does not even claim a therapeutic use for Ra-X-Rb compound comprising peptide 5 in claims 3 or 4.

More importantly, there does not appear to be any teaching in the '216 patent that would motivate one of skill in the art to select [D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}[hGRF(1-29)-NH_2 for use in a pharmaceutical composition over any of the other hGHRH analogues described therein (compare, for example, the IC_{50} value or the relative affinity of compound 8 with those of the remaining analogues in Table 11).

Additionally, growth hormone release activity for compound 8 does not appear to have been investigated in the '216 patent, nor does the reference provide adequate support for pharmaceutical composition stimulating secretion or synthesis of growth hormone in a mammal. Applicant respectfully submits that it is impossible to predict *a priori* from the disclosure of the '216 patent whether a pharmaceutical composition comprising or consisting of peptide 5 or a paharmaceutically active salt thereof would be capable of stimulating the synthesis or secretion of growth hormone in a human or animal subject.

Applicant respectfully submits that the '216 patent fails to provide a reasonable expectation that a pharmaceutical composition comprising compound 8 would successfully provide the desired characteristics of the instantly claimed pharmaceutical compositions. As such,

Applicant respectfully submits that the '216 patent fails to establish a *prima facie* case of obviousness against the claims.

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art and not based on applicant's disclosure. *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). (*Emphasis added*).

The '216 patent fails to provide any indication or suggestion that the compound in question (i.e., D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}[hGHRH(1-29)-NH_2) binds to the human GHRH receptor with >900X affinity than it binds to the rat GHRH receptor. The Applicant directs the Examiner's attention to Table 1 of the instant specification (note, the compound referred to in the '216 as compound 8 is referred to in the instant case as compound 5). When compound 5 is applied to BHK cells expressing recombinant human GHRH receptor (hGHRH-R), it can be seen that the relative binding affinity for the human GHRH-R is increased by almost 3-logs. The specification, Table 1, compound 5 teaches, in part:

No.	Structure	Relative binding affinity in rat anterior pituitary	Relative binding affinity in hGHRH-R BHK-expressing cells
5	[D-Ala^2, D-Tyr^{10}, D-Ala^{15}, Lys^{22}[hGRF(1-29)-NH_2	1.04 ± 0.40	939 ± 249

Applicant further refers the Examiner to paragraph [0061-0062] of the instant specification, which states in part:

> [0061] Initial selection of a candidate from the original 14 polysubstituted GHRH analogues described in the U.S. Pat. No. 5,854,216 was based upon in vitro data on receptor affinity in 2-month old male Sprague Dawley rat anterior pituitary preparations. The new invention is based on the affinity of selected GHRH analogues for the human GHRH receptor (hGHRH-R) in baby hamster kidney (BHK) cells transfected with hGHRH-R, and on resistance to proteolysis in rat serum, human plasma or human serum. More precisely, the preferred drug candidates were selected, as compared hGHRH(1-29)-NH_2, for: i--their increased relative binding affinity to hGHRH(1-44)-NH_2 binding sites in rat anterior pituitary in vitro as well as to hGHRH-R in BHK-expressing cells in vitro;

> and ii--their relative resistance to proteolysis in vitro.
> [0062] As can be noted from Table 1 below, the relative binding affinity of the synthetic peptides with the rat GHRH receptor is not predictive of the relative binding affinity with the human receptor. As will be noted, from this point forward, GHRH analogues as presented in Table 1 will be referred to as GHRH analogues # 1 to 5. (*Emphasis added*)

The '216 patent is silent on a GHRH analogues having the feature and uses as presently claimed. Applicant submits that a practitioner having ordinary skill in the art would not have been motivated, among all of the species taught in the '216 patent, to select the species [D-Ala^{2}, D-Tyr^{10}, D-Ala^{15}, Lys^{22}[hGRF(1-29)-NH_2 for use in a pharmaceutical composition or for therapeutic modality.

In light of the above, Applicant respectfully submits that claims 17 – 30 and 39 and the new claims are unobvious and patentable over the teachings of the '216 patent, and respectfully requests the withdrawal of the 35 USC §103 rejections.

D. Conclusion

Applicant submits that the claims are in condition for allowance. Favorable reconsideration is respectfully requested.

Applicant respectfully requests a three-moth extension of time for submission of this response. If any additional extensions of time are required, Applicant hereby requests the appropriate extension of time. If any fees are required, or have been overpaid, please appropriately charge, or credit, those fees to Meyertons, Hood, Kivlin, Kowert & Goetzel, P.C. Deposit Account Number 50-1505/6165-09602/EBM.

Respectfully submitted,

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Date: March 24, 2008